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REMARKS

Reconsideration of the above referenced application is respectfully requested. Upon entry of the foregoing amendment, Claims 72-87 are presently pending. Claims 1-71 and Claims 88 -95 have been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of the cancelled claims in one or more continuation or divisional application. No new matter has been introduced and entry of this amendment is respectfully requested.

Rejection under 35 U.S.C. §112, second paragraph.

Claim 87 stands rejected under 35 U.S.C. 112, second paragraph, as incomplete for lacking a period.

Applicants respectfully submit that the grounds for the rejection have been obviated by the amendments submitted herein. Withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Rejection under 35 U.S.C. §112, first paragraph, written description.

Claims 72-87 stand rejected under 35 U.S.C. 112 first paragraph as lacking written description. Specifically, the Examiner alleges that the claims contain subject matter that is not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed.

More specifically, the Office Action states that Claims 72-87 require an oncolytic virus comprising a urothelium specific promoter and that the specification discloses a single example of such a promoter in recombinant adenovirus CG8840 and that the specification does not disclose any other promoter specific to the bladder epithelium.

Applicants disagree and respectfully submit that the specification meets Applicants' burden under 35 U.S.C. 112, first paragraph, and provides a sufficient number of species to support the presently pending claims.

The guidelines for determining compliance with 35 U.S.C. 112 note that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. Applicants note that recitation in a claim of a generic element, for example a transcriptional response element, does not require that the specification list each and every promoter that might be used with the invention. Rather, one may rely on the many promoters known in the art to be useful in initiation transcription of a proximal gene. Indeed, as set forth in the MPEP: a patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc*., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

Applicants submit that the invention is not limited to a single urothelium specific promoter. Replication competent oncolytic viruses with other different promoters are also effective in transduction of cells of the bladder epithelium. The 1.132 declaration of David Frey (submitted herewith) provides data for transduction of cells of the bladder epithelium, following pretreatment of the luminal surface of the bladder with a transduction enhancing agent. The declaration shows that two additional and different replication competent oncolytic viruses, Ar20-1004 and CG0070, were used to successfully transduce the bladder epithelium following pretreatment with a transduction enhancing agent. Ar20-1004 is a replication competent adenovirus modified to express the murine cytokine granulocyte macrophage colony stimulatory factor (GM-CSF) and CG0070 is a similar replication competent adenovirus modified to express human GM-CSF. In both viruses, the adenoviral E1a promoter of wild type adenovirus is replaced with the human E2F-1 promoter. When rat bladders were pretreated with a transduction enhancing agent, dodecyl maltoside (DDM), prior to transduction with Ar20-1004, the level of

GM-CSF detected in rat urine was more than 18 times the amount detected when bladders were not pretreated prior to transduction. See paragraphs 28-29 of the David Frey declaration.

Given the enhanced transduction efficiency when bladders are pretreated with a transduction enhancing agent, DDM, prior to instillation of replication competent adenovirus into the bladder, a phase I human clinical study was initiated. In the clinical protocol, the bladders of all patients were pretreated with DDM, prior to instillation of CG0070. Patients were assessed for adverse events and laboratory measures of toxicity. Cystoscopic examination of 3 patients day 8 after treatment with 10^{12}vp revealed inflammation and tumor regression. A complete response at week 12+ after treatment was reported in a patient with transition cell carcinoma (TCC) treated with 10^{12}vp. The results provide support for efficacy of the claimed transduction enhancing agents in transduction of the bladder epithelium with two oncolytic adenoviruses which differ in structure and mode of infectivity. See paragraph 30 of the David Frey declaration.

One of ordinary skill in the art would be informed by the teachings of the subject specification, as to how to make and use the genus of replication competent adenovirus for transducing bladder epithelium cells. In view of the above amendments and remarks, withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §103(a).

In the Office Action, the Examiner sets forth a number of grounds for rejection under 35 USC §103, each of which is discussed in detail as they apply to the current claims, below.

Claims 72, 74 and 83-85 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious over Zhang et al. (Cancer Res. 62:3743-3750, 2002) in view of Conner et al. (Gene Therapy 8:41-48, 2001).

On page 5 of the Office Action, Zhang et al. is cited as allegedly teaching that adenovirus CG8840 was a urothelium-specific adenovirus variant that eliminates bladder tumors when administered in combination with docetaxel.

Conner et al. is cited as allegedly teaching that adenoviral infection of the urothelium was improved when adenovirus was delivered to the urothelium with octyl-beta-D-glucopyranoside (table 1, page 42).

The Office Action further states that it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Zhang et al. by applying adenovirus to the luminal surface of a bladder, as taught by Conner et al., in order to treat bladder cancer.

The Examiner acknowledges that Conner et al. did not teach sequential addition of octyl-beta-D-glucopyranoside followed by adenovirus, but instead added them simultaneously and that the process of Conner et al. differs from the current claims with respect to the wash step and the amount of virus. However, the Examiner cites to MPEP 2144.04 (IV)(C) in taking the position that selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results and that variables such as volume of virus solution and number of viral particles are not sufficient to support patentability unless there is evidence to support the fact that such concentration or temperature is critical, alleging that such variables can be optimized by routinc experimentation. Applicants respectfully disagree.

To establish a prima facie case of obviousness the prior art reference (or references when combined) must teach or suggest all of the claim limitations. In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991) and MPEP § 2142. Moreover, when applying 35 U.S.C. § 103, the following tenets of patent law must be adhered to: (A) The claimed invention must be considered as a whole; (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (D) A reasonable expectation of success is the standard with which obviousness is determined. Hodosh v. Block Drug Co., Inc., 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

As stated in MPEP §2142, "the examiner bears the initial burden of factually supporting any prima facie conclusion of obviousness. If the examiner does not produce a prima facie case, the applicant is under no obligation to submit evidence of nonobviousness." The Examiner has not met his burden in this respect, however, in the

interest of expediting the prosecution of this case, Applicants submit the following arguments.

Conner et al. is cited as allegedly teaching that adenoviral infection of the urothelium was improved when adenovirus was delivered to the urothelium with octyl-beta-D-glucopyranoside (a monosaccharide with a C8 side chain). In contrast, the present invention relies on the use of a disaccharide, having a lipophilic substituent and a side chain with from 10 to 14 carbons or a cyclohexylhexyl group to enhance adenoviral transduction of the bladder epithelium. As indicated on page 41, lines 4-5 of the specification, n-dodecyl-beta-D-glucopyranoside showed little or no enhancement of bladder transduction.

The declaration of David Frey (provided herewith) shows that contrary to the teachings of Conner et al., no transduction of bladder epithelium, was observed when rat bladders were pretreated with octyl-beta-D-glucopyranoside (paragraphs 13, 17, 22 and Exhibit B) followed by exposure to a replication competent (oncolytic) virus. The concentration of octyl-beta-D-glucopyranoside is not disclosed in Conner et al., the octyl-beta-D-glucopyranoside was mixed with replication-deficient adenovirus and exposed to the bladder epithelium for 45 minutes (paragraphs 19, 20, 24 and 25 of the David Frey declaration).

As stated in paragraph 21 of the Frey declaration, if one of skill in the art relied on Conner et al., they would have tested monosaccharides with C8 side chains, e.g., octyl-beta-D-glucopyranoside, shown in Table 1 of Conner et al., in order to enhance transduction of the bladder epithelium. As shown by the data presented with the Frey declaration, if the inventors had relied on Conner et al., they would have seen no transduction of the bladder epithelium and would not have been motivated to look for effective bladder transduction enhancing agents with a chemical structure similar to octyl-beta-D-glucopyranoside (i.e. the class of alkyl monosaccharides or compounds with C8 side chains).

It follows that Conner et al., not only does not render the current invention obvious. In fact, the reference teaches away from the subject matter of the present invention.

Zhang et al. do not teach administration to the luminal surface of the bladder or the use of a transduction enhancing agent.

It follows that the combination of Zhang et al. and Conner et al. does not teach or suggest a method of treating cancer of the bladder comprising contacting the luminal surface of the bladder with a pretreatment composition comprising a transduction enhancing agent having the general formula I with a side chain (R1) comprising from 10 to 14 carbons or a cyclohexylhexyl group, followed by exposure to a replication competent oncolytic virus.

Hence, the combined references do not teach or suggest all of the claim limitations. Therefore, one of skill in the art relying on the combination of Zhang et al. and Conner et al. would not have a reasonable expectation of success in practicing the present invention, a *prima facie* case of obviousness has not been established and the rejection should be withdrawn.

Claims 72, 74, and 85 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious over Watanabe et al. (Int .J. Cancer 92:712-171, 2001) in view of Conner et al. (Gene Therapy 8:41-48, 2001) and Mullen et al. (Oncologist 7:106-119, 2002).

Watanabe et al. is cited as allegedly teaching methods of treating bladder cancer with replication deficient adenovirus carrying a suicide gene (ras) in a mouse model of bladder cancer, that the virus was instilled intravesically and inhibited the growth of superficial tumors. The Office Action states that Watanabe et al. did not teach an oncolytic virus or use of a transduction enhancing agent.

Conner et al. is described above and is relied upon as teaching that transduction of bladder tissue could be improved by treatment of the urothelium with octyl-beta-D-glucopyranoside.

Mullen et al. is cited as allegedly teaching that oncolytic viruses expressing therapeutic transgenes offered a distinct advantage over analogous replication defective gene therapy vectors because the virus amplifies itself through several rounds of replication allowing an increase in gene expression leading to an amplified anti tumor effect.

On page 7 and 8, the Office Action concludes that it would have been obvious to one of skill in the art at the time of the invention to modify the method of Watanabe et al. by treating mouse bladders with octyl-beta-D-glucopyranoside and to substitute replication competent adenoviruses for replication defective ones. Applicants respectfully disagree.

Watanabe et al. did not teach an oncolytic virus or use of a transduction enhancing agent.

As set forth above, Conner et al. teaches enhanced transduction of the bladder epithelium by a replication defective adenovirus when the virus is mixed with octyl-beta-D-glucopyranoside. The declaration of David Frey (provided herewith) shows that contrary to the teachings of Conner et al., no transduction of bladder epithelium was observed by the inventors when rat bladders were pretreated with octyl-beta-D-glucopyranoside followed by exposure to a replication competent (oncolytic) virus (paragraphs 13, 17, 22 and Exhibit B of Frey declaration). See also page 41, lines 4-5 of the instant specification.

Conner et al. is cited as allegedly teaching that adenoviral infection of the urothelium was improved when adenovirus was delivered to the urothelium with octyl-beta-D-glucopyranoside (a monosaccharide with a C8 side chain). In contrast, the present invention relies on the use of a disaccharide, having a lipophilic substituent and a side chain with from 10 to 14 carbons or a cyclohexylhexyl group to enhance adenoviral transduction of the bladder epithelium. Hence, Conner et al. teaches away from the present invention.

Paragraph 21 of the Frey declaration states that if one of skill in the art relied on Conner et al., they would have tested monosaccharides with C8 side chains, e.g., octyl-beta-D-glucopyranoside, shown in Table 1 of Conner et al., in order to enhance transduction of the bladder epithelium. If the inventors had relied on Conner et al., they would have seen no transduction of the bladder epithelium and would not have been motivated to look for effective bladder transduction enhancing agents with a chemical structure similar to octyl-beta-D-glucopyranoside (i.e. the class of alkyl monosaccharides or compounds with C8 side chains).

The combination of Watanabe et al., Conner et al. and Mullen et al. does not teach or suggest a method of treating cancer of the bladder comprising contacting the luminal surface of the bladder with a pretreatment composition comprising a transduction enhancing agent having a disaccharide structure with a lipophilic substituent and a side chain with from 10 to 14 carbons or a cyclohexylhexyl group which enhances transduction of the bladder epithelium with a replication competent (oncolytic) virus. Hence, the combined references do not teach or suggest all of the claim limitations.

Therefore, one of skill in the art relying on the combination of Watanabe et al., Conner et al. and Mullen et al. would not have a reasonable expectation of success in practicing the present invention and a *prima facie* case of obviousness has not been established and the rejection should be withdrawn.

Claims 72, 74, and 85 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious over Watanabe et al. (Int .J. Cancer 92:712-171, 2001) in view of Conner et al. (Gene Therapy 8:41-48, 2001) and Mullen et al. (Oncologist 7:106-119, 2002).

Watanabe et al. is cited as allegedly teaching methods of treating bladder cancer with replication deficient adenovirus carrying a suicide gene (ras) in a mouse model of bladder cancer, that the virus was instilled intravesically and inhibited the growth of superficial tumors. The Office Action states that Watanabe et al. did not teach an oncolytic virus or use of a transduction enhancing agent.

Conner et al. is described above and is relied upon as teaching that transduction of bladder tissue could be improved by treatment of the urothelium with octyl-beta-D-glucopyranoside.

Mullen et al. is cited as allegedly teaching that oncolytic viruses expressing therapeutic transgenes offered a distinct advantage over analogous replication defective gene therapy vectors because the virus amplifies itself through several rounds of replication allowing an increase in gene expression leading to an amplified anti tumor effect.

On page 7 and 8, the Office Action concludes that it would have been obvious to one of skill in the art at the time of the invention to modify the method of Watanabe et al. by treating mouse bladders with octyl-beta-D-glucopyranoside and to substitute replication competent adenoviruses for replication defective ones. Applicants respectfully disagree.

Watanabe et al. did not teach an oncolytic virus or use of a transduction enhancing agent.

As set forth above, Conner et al. teaches enhanced transduction of the bladder epithelium by a replication defective adenovirus when the virus is mixed with octyl-beta-D-glucopyranoside. The declaration of David Frey (provided herewith) shows that contrary to the teachings of Conner et al., no transduction of bladder epithelium was observed by the inventors when rat bladders were pretreated with octyl-beta-D-glucopyranoside followed

by exposure to a replication competent (oncolytic) virus (paragraphs 13, 17, 22 and Exhibit B of Frey declaration). See also page 41, lines 4-5 of the instant specification.

Conner et al. is cited as allegedly teaching that adenoviral infection of the urothelium was improved when adenovirus was delivered to the urothelium with octyl-beta-D-glucopyranoside (a monosaccharide with a C8 side chain). In contrast, the present invention relies on the use of a disaccharide, having a lipophilic substituent and a side chain with from 10 to 14 carbons or a cyclohexylhexyl group to enhance adenoviral transduction of the bladder epithelium.

Paragraph 21 of the Frey declaration states that if one of skill in the art relied on Conner et al., they would have tested monosaccharides with C8 side chains, e.g., octyl-beta-D-glucopyranoside, shown in Table 1 of Conner et al., in order to enhance transduction of the bladder epithelium. If the inventors had relied on Conner et al., they would have seen no transduction of the bladder epithelium and would not have been motivated to look for effective bladder transduction enhancing agents with a chemical structure similar to octyl-beta-D-glucopyranoside (i.e. the class of alkyl monosaccharides or compounds with C8 side chains).

To establish a prima facie case of obviousness the prior art reference (or references when combined) must teach or suggest all of the claim limitations. In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991) and MPEP § 2142. Moreover, when applying 35 U.S.C. § 103, the following tenets of patent law must be adhered to: (A) The claimed invention must be considered as a whole; (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (D) A reasonable expectation of success is the standard with which obviousness is determined. Hodosh v. Block Drug Co., Inc., 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

The combination of Watanabe et al., Conner et al. and Mullen et al. does not teach or suggest a method of treating cancer of the bladder comprising contacting the luminal surface of the bladder with a pretreatment composition comprising a transduction enhancing agent having a disaccharide structure with a lipophilic substituent and a side chain with from 10 to 14 carbons or a cyclohexylhexyl group which enhances transduction of the bladder epithelium with a

replication competent (oncolytic) virus. Hence, the combined references do not teach or suggest all of the claim limitations. Further, Conner et al. teaches away from the present invention and thus one of skill in the art relying on the combination of Watanabe et al., Conner et al. and Mullen et al. would not have a reasonable expectation of success in practicing the present invention.

Therefore, one of skill in the art relying on the combination of Watanabe et al., Conner et al. and Mullen et al. would not have a reasonable expectation of success in practicing the present invention and a *prima facie* case of obviousness has not been established and the rejection should be withdrawn.

Claims 72-81 and 85 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious over Watanabe et al. (Int .J. Cancer 92:712-171, 2001) in view of Conner et al. (Gene Therapy 8:41-48, 2001), Mullen et al. (Oncologist 7:106-119, 2002) and Boer et al. (Biocehm. Biophys. Res. Comm. 166(1): 91-98, 1983).

Watanabe et al., Conner et al. and Mullen et al. are described above. On page 9, the Office Action states that the combination of Watanabe et al., Conner et al. and Mullen et al. render obvious a method of treating superficial bladder cancer with octyl-beta-D-glucopyranoside and exposing the surface of the bladder to an oncolytic virus. The Examiner acknowledges that the combination of Watanabe et al., Conner et al. and Mullen et al. do not teach a disaccharide comprising a lipophilic substituent.

Boer et al. is cited as allegedly teaching that dodecyl-beta-D-maltopyranoside is a detergent with performance characteristics similar to octyl-beta-D-glucopyranoside for solublizing vasopressin receptors from membranes.

On page 9 and 10, the Office Action concludes that it would have been obvious to one of skill in the art at the time of the invention to use dodecyl-beta-D-maltoside to improve adenoviral transduction of the bladder epithelium in the method of Watanabe et al. The Office Action states that dodecyl-beta-D-maltoside was a detergent with performance characteristics similar to octyl-beta-D-glucopyranoside which was used by Conner et al. to enhance bladder transduction. Applicants respectfully disagree.

The declaration of David Frey shows that the inventors tested a large number of detergents including standard agents such as polymer-based detergents (i.e. Tweens) and mono-, di-, or poly-saccharides having a lipophilic substituent were tested to evaluate their efficacy as transduction enhancing agents for conditionally replication-competent oncolytic viruses in order to evaluate their utility in intravesicular therapy of bladder cancer (paragaraph 6 of Frey declaration).

A number of studies were performed and it was determined that a class of compounds is effective for pretreatment of the bladder urothelium, permitting efficient adenoviral infection, by "permeabilizing" (not dissolving) a "mucous" membrane composed of the glycosaminoglycan (GAG) layer, which is not a cell membrane (paragaraph 8 of Frey declaration). The data disclosed in the subject patent application was later published (Ramesh et al., Mol. Ther. 10(4):697-705, 2004). The present invention is based on the results of these studies.

All of the compounds which facilitated a 0 transduction efficacy are monosaccharides with an n-dodecyl (C12) side chain, an n-octyl (C8) side chain, or a phenyl (C6) side chain; disaccharides with an n-octyl (C8) side chain, sulfates with an n-octyl (C8) or n-tetradecyl (C14) side chain; glycerol-based agents, Tween 20, Tween 80 or PBS (paragaraph 17 of Frey declaration).

The declaration of David Frey also shows that contrary to the teachings of Conner et al., no transduction of bladder epithelium, was observed when rat bladders were pretreated with octyl-beta-D-glucopyranoside (paragraphs 13, 17, 22 and Exhibit B) followed by exposure to a replication competent (oncolytic) virus. The concentration of octyl-beta-D-glucopyranoside is not disclosed in Conner et al., the octyl-beta-D-glucopyranoside was mixed with replication-deficient adenovirus and exposed to the bladder epithelium for 45 minutes (paragraphs 19, 20, 24 and 25 of the David Frey declaration).

As stated in paragraph 21 of the Frey declaration, if one of skill in the art relied on Conner et al., they would have tested monosaccharides with C8 side chains, e.g., octyl-beta-D-glucopyranoside, shown in Table 1 of Conner et al., in order to enhance transduction of the bladder epithelium. As shown by the data presented with the Frey declaration, if the inventors had relied on Conner et al., they would have seen no transduction of the bladder epithelium and

would not have been motivated to look for effective bladder transduction enhancing agents with a chemical structure similar to octyl-beta-D-glucopyranoside (i.e. the class of alkyl monosaccharides or compounds with C8 side chains).

It follows that Conner et al., not only does not render the current invention obvious. In fact, the reference teaches away from the subject matter of the present invention.

As set forth above, the combination of Watanabe et al., Conner et al. and Mullen et al. do not teach or suggest all of the claim limitations. Further, Conner et al. teaches away from the present invention. Boer et al. does not make up for this deficiency and thus one of skill in the art relying on the combination of Watanabe et al., Conner et al., Mullen et al. and Boer et al. would not have a reasonable expectation of success in practicing the present invention.

Therefore, a *prima facie* case of obviousness has not been established and the rejection should be withdrawn.

Claims 72-74, 82 and 85 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious over Watanabe et al. (Int .J. Cancer 92:712-171, 2001) in view of Conner et al. (Gene Therapy 8:41-48, 2001), Mullen et al. (Oncologist 7:106-119, 2002) and Sedzik et al. (NeuroReport 11(11) 2559-2563, 2000).

Watanabe et al., Conner et al. and Mullen et al. are described above. On page 12, the Office Action states that the combination of Watanabe et al., Conner et al. and Mullen et al. render obvious a method of treating superficial bladder cancer with octyl-beta-D-glucopyranoside and exposing the surface of the bladder to an oncolytic virus. The Examiner acknowledges that the combination of Watanabe et al., Conner et al. and Mullen et al. do not teach a disaccharide comprising a lipophilic substituent, i.e. a cyclohexylhexyl moiety.

Sedzik et al. is cited as allegedly teaching dodecyl-beta-D-maltopyranoside, decyl-beta-D-maltopyranoside, cyclohexyl pentyl-beta-D-maltoside, cyclohexyl hexyl-beta-D-maltoside, octyl-beta-D-thioglucopyranoside and heptyl-beta-D-thioglucopyranoside as detergents with performance characteristics similar to octyl-beta-D-glucopyranoside for solublizing PNS myelin membrane proteins.

On pages 13 and 14, the Office Action concludes that it would have been obvious to one of skill in the art at the time of the invention to use dodecyl-beta-D-maltopyranoside, decyl-beta-

D-maltopyranoside, cyclohexyl pentyl-beta-D-maltoside, cyclohexyl hexyl-beta-D-maltoside as a detergent to enhance transduction of the bladder epithelium in the invention of Watanabe as modified by Conner and Mullen. Applicants respectfully disagree.

One of skill in the art would appreciate that the performance characteristics of dodecyl-beta-D-maltopyranoside, decyl-beta-D-maltopyranoside, cyclohexyl pentyl-beta-D-maltoside, cyclohexyl hexyl-beta-D-maltoside, octyl-beta-D-thioglucopyranoside and heptyl-beta-D-thioglucopyranoside as detergents for solublizing PNS myelin membrane proteins is not suggestive of the relative ability of various compounds to enhance transduction of the bladder epithelium by an oncolytic adenovirus; in particular in light of data in the instant specification (page 41, lines 4-5) which states that n-dodecyl-beta-D-glucopyranoside showed little or no enhancement of bladder transduction, while treatment of the bladder epithelium with dodecyl-beta-D-maltoside and 6-cyclohexylhexyl-beta-D-maltoside resulted in a high level of transduction (page 37, line 24 through page 38, line1).

Furthermore as set forth above, Conner et al. teaches away from the present invention and paragraph 21 of the Frey declaration states that if one of skill in the art relied on Conner et al., they would have tested monosaccharides with C8 side chains, e.g., octyl-beta-D-glucopyranoside, shown in Table 1 of Conner et al., in order to enhance transduction of the bladder epithelium. If the inventors had relied on Conner et al., they would have seen no transduction of the bladder epithelium and would not have been motivated to look for effective bladder transduction enhancing agents with a chemical structure similar to octyl-beta-D-glucopyranoside (i.e. the class of alkyl monosaccharides or compounds with C8 side chains).

As set forth above, the combination of Watanabe et al., Conner et al. and Mullen et al. do not teach or suggest all of the claim limitations. Further, Conner et al. teaches away from the present invention. Sedzik et al. does not make up for this deficiency and thus one of skill in the art relying on the combination of Watanabe et al., Conner et al., Mullen et al. and Sedzik et al. would not have a reasonable expectation of success in practicing the present invention.

Therefore, a *prima facie* case of obviousness has not been established and the rejection should be withdrawn.

Claims 72-74, 82 and 85 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious over Watanabe et al. (Int .J. Cancer 92:712-171, 2001) in view of Conner et al. (Gene Therapy 8:41-48, 2001), Mullen et al. (Oncologist 7:106-119, 2002) and Amiel et al. (WO 02/40630).

Watanabe et al., Conner et al. and Mullen et al. are described above. On pages 15 and 16, the Office Action states that the combination of Watanabe et al., Conner et al. and Mullen et al. render obvious a method of treating superficial bladder cancer with octyl-beta-D-glucopyranoside and exposing the surface of the bladder to an oncolytic virus. The Examiner acknowledges that the combination of Watanabe et al., Conner et al. and Mullen et al. do not teach a disaccharide comprising a lipophilic substituent, particularly an alkanoic acid residue.

Amiel et al. is cited as allegedly teaching that a variety of detergents such as sucrose monolaureate and dodecyl maltoside, as well as TWEEN-20 and TWEEN-80 could be used as alternatives to octyl-beta-D-glucopyranoside including sucrose monolaurate and dodecyl maltoside.

On pages 16 and 17, the Office Action concludes that it would have been obvious to one of skill in the art at the time of the invention to use TWEEN-20 and TWEEN-80 to improve adenoviral transduction of the bladder epithelium as alternatives to octyl-beta-D-glucopyranoside. Applicants respectfully disagree.

As set forth above, the declaration of David Frey shows that the inventors tested a large number of detergents including standard agents such as polymer-based detergents (i.e. Tweens) and mono-, di-, or poly-saccharides having a lipophilic substituent were tested to evaluate their efficacy as transduction enhancing agents for conditionally replication-competent oncolytic viruses in order to evaluate their utility in intravesicular therapy of bladder cancer (paragaraph 6 of Frey declaration).

A number of studies were performed and it was determined that a class of compounds is effective for pretreatment of the bladder urothelium, permitting efficient adenoviral infection, by "permeabilizing" (not dissolving) a "mucous" membrane composed of the glycosaminoglycan (GAG) layer, which is not a cell membrane (paragaraph 8 of Frey declaration). The data disclosed in the subject patent application was later published (Ramesh et al., Mol. Ther. 10(4):697-705, 2004). The present invention is based on the results of these studies.

5. All of the compounds which facilitated a 0 transduction efficacy are monosaccharides with an n-dodecyl (C12) side chain, an n-octyl (C8) side chain, or a phenyl (C6) side chain; disaccharides with an n-octyl (C8) side chain, sulfates with an n-octyl (C8) or n-tetradecyl (C14) side chain; glycerol-based agents, Tween 20, Tween 80 or PBS (paragaraph 17 of Frey declaration).

The declaration of David Frey also shows that contrary to the teachings of Conner et al., no transduction of bladder epithelium, was observed when rat bladders were pretreated with octyl-beta-D-glucopyranoside (paragraphs 13, 17, 22 and Exhibit B) followed by exposure to a replication competent (oncolytic) virus. The concentration of octyl-beta-D-glucopyranoside is not disclosed in Conner et al., the octyl-beta-D-glucopyranoside was mixed with replication-deficient adenovirus and exposed to the bladder epithelium for 45 minutes (paragraphs 19, 20, 24 and 25 of the David Frey declaration).

As stated in paragraph 21 of the Frey declaration, if one of skill in the art relied on Conner et al., they would have tested monosaccharides with C8 side chains, e.g., octyl-beta-D-glucopyranoside, shown in Table 1 of Conner et al., in order to enhance transduction of the bladder epithelium. As shown by the data presented with the Frey declaration, if the inventors had relied on Conner et al., they would have seen no transduction of the bladder epithelium and would not have been motivated to look for effective bladder transduction enhancing agents with a chemical structure similar to octyl-beta-D-glucopyranoside (i.e. the class of alkyl monosaccharides or compounds with C8 side chains).

As set forth above, the combination of Watanabe et al., Conner et al. and Mullen et al. do not teach or suggest all of the claim limitations. Further, Conner et al. and Amiel both teach away from the present invention.

Therefore, one of skill in the art relying on the combination of Watanabe et al., Conner et al., Mullen et al. and Amiel et al. would not have a reasonable expectation of success in practicing the present invention and a *prima facie* case of obviousness has not been established and the rejection should be withdrawn.

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CONCLUSION

In light of the above, Applicants submit that this application is now in condition for allowance and therefore request favorable consideration. If any issues remain which the Examiner feels may be best resolved through a personal or telephonic interview, the Examiner is respectfully requested to contact Applicants' counsel, Linda R. Judge at (415) 836-2586.

Respectfully submitted,

Date: 2/8/07

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